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Impact of *PPAR-γ2 pro12Ala* Gene Polymorphism and Susceptibility of Type 2 Diabetes Mellitus in Patients Visiting Gondar University Teaching Hospital

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Abstract

Type 2 diabetes mellitus (T2DM) is characterized by hyperglycemia that can occur through mechanisms such as; impaired insulin secretion, insulin resistance in peripheral tissues and increased glucose output by liver. Type 2 diabetes clearly represents a multifactorial disease, and several findings indicate that multiple genetic and environmental factors are important contributing factor involved in the pathogenesis of this disease. Recently great emphasis has been given to genetical factors to combat the disease. The discovery of T2DM-associated genes through genome wide association studies (GWAS) has provided insight into the genetic architecture of T2DM, and several genes have been reported to be related to T2DM susceptibility. One of these genes is PPARG -γ2 (Peroxisome proliferator-activated receptors –gamma), which has been confirmed to be a potential type 2 diabetic risk for different ethnic populations. It has been reported in the literature that, at the molecular level, PPAR-γ2Pro12 Ala gene polymorphism; the Pro allele has been associated with increased risk of diabetic 2 in different population. On the other hand, the Ala allele of the PPAR-γ2 gene has been reported to be strongly associated with reduced risk of the disease. The aim of the present study was to assess the impact of PPAR-γ2 gene polymorphism on risk of diabetic type 2 patients visiting Gondar University Teaching Hospital. One hundred diabetic-2 patients and an equal number of age and sex matched control groups were recruited for this case control study from the teaching hospital of the university.

Keywords: *Diabetic mellitus, Genetic polymorphisms, pro12Ala, PPAR-γ2*

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INTRODUCTION

Type 2 diabetes is an increasingly common, serious metabolic disorder with a substantial inherited component. It is characterized by defects in both insulin secretion and action. Progress in identification of specific genetic variants predisposing to the disease has been limited. Type 2 diabetes is a serious metabolic disease associated with an increased risk of premature death and substantial disability, largely mediated through its adverse effects on the vasculature. The prevalence of the disease is increasing, and the World Health organization estimate suggests that by 2025 there will be 300 million affected individuals worldwide. The disorder is characterized by a combination of impaired insulin secretion and insulin action, both of which precede and predict the onset of disease. Through its adverse impact on insulin action, obesity is a major risk factor for the disease.

Although environmental factors, both post- and prenatal, play an important role in determining the risk of disease, a substantial body of evidence supports the notion that disease susceptibility is influenced by inherited factors [1]. While the molecular basis for several uncommon Mendelian forms of Type 2 diabetes have been defined [2–4], the nature and range of allelic variants conferring susceptibility to the more common forms of this disorder remain poorly defined. The gene PPAR-γ2 has been linked with both positive and negative associations in different ethnic back grounds.

Studies on the association of the *Pro12Ala* polymorphism of *PPAR-γ2* with diabetes have revealed extensive population-dependent variations. However, association of these polymorphisms with T2D and its individual components has not been investigated in

Ethiopian population. Therefore, this study attempts to reveal this polymorphism in north Gondar administrative zone.

MATERIALS AND METHODS

For this case control study 100 clinically diagnosed diabetic II male and female patients in Gondar University teaching hospitals whose age group ranges from 35–60 were recruited. An equal number of sex and age matched volunteer control groups who are confirmed to be free from any kind of disease symptoms and free from diabetic 2 through clinical diagnosis were also involved in the study from the same geographical area. Blood samples of study subjects were collected by EDTA coated vacutanous tubes and transported to the laboratory by ice box and stored in -20 until DNA isolation were conducted. DNA was isolated by standardized phenol chloroform method. Appropriate primers (Forward primer 5`- CAAGCCCAGTCCTTTCTGTG-3`, and Reverse primer 5`-AGTGAAGGAATCGCTTTCCG-3`), PCR reaction and condition will be utilized to amplify the gene *PPAR-Y2* by the polymerase chain reaction. The enzyme HPA II was used to differentiate the *pro* and *Ala* alleles by the presence and absence of a restriction site through the Restriction Fragment Length Polymorphism (RFLP) techniques. The Pcr products were analyzed by 2% agarose gel electrophoresis. Valuable data regarding study subjects such as: Age, sex, family history, weight, occupation, inhabitant (Urban vs. Rural) were registered by specially designed questioner and recorded. The association of the *pro*12 *Ala* gene polymorphism of *PPAR-γ*-gene with risk of diabetic 2 were computed with appropriate softwares (SPSS 11.5) and EPI-info version 3.1(center for disease control and prevention, USA) as per the recommendation of WHO. This study was approved by the ethical committee of The Faculty of Natural and computational Sciences. Moreover, informed consents were obtained from both cases and controls.

RESULTS

The demographic characteristics of the study subjects are given in Figure 1. The mean age among cases was 45±9.8 and it was 43±7.5 in controls. Sixty five percent of cases were from urban area and the rest were from rural areas. The controls were all from urban area. There was no statistically significance difference between the age of cases and controls (p>0.05). As far as age is concerned 68% of cases were males. In controls the same numbers of males were taken because this sample is taken after gender of cases was known.

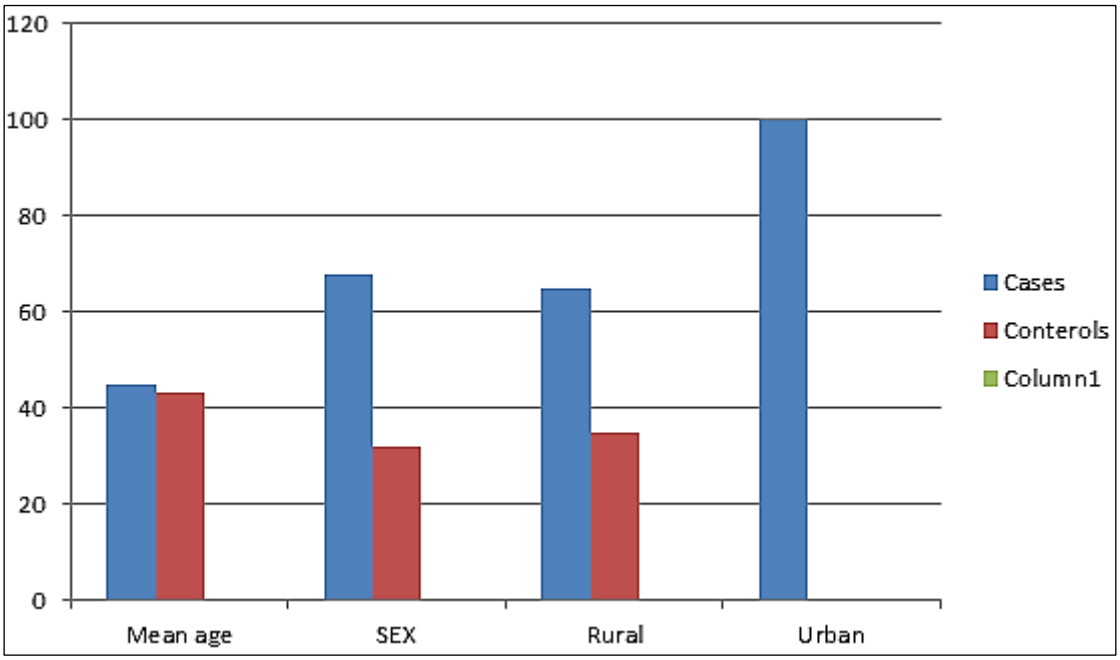

Fig. 1: *Demographic Characteristics of Study Subjects.*

The percentages of the three genotypes in cases were 77,21 and 2 for *Pro/Pro*, *Pro/Ala*, *Ala/Ala*, respectively. In controls it was 72,18 and 5 percentages for three genotypes, respectively (Figure 2).

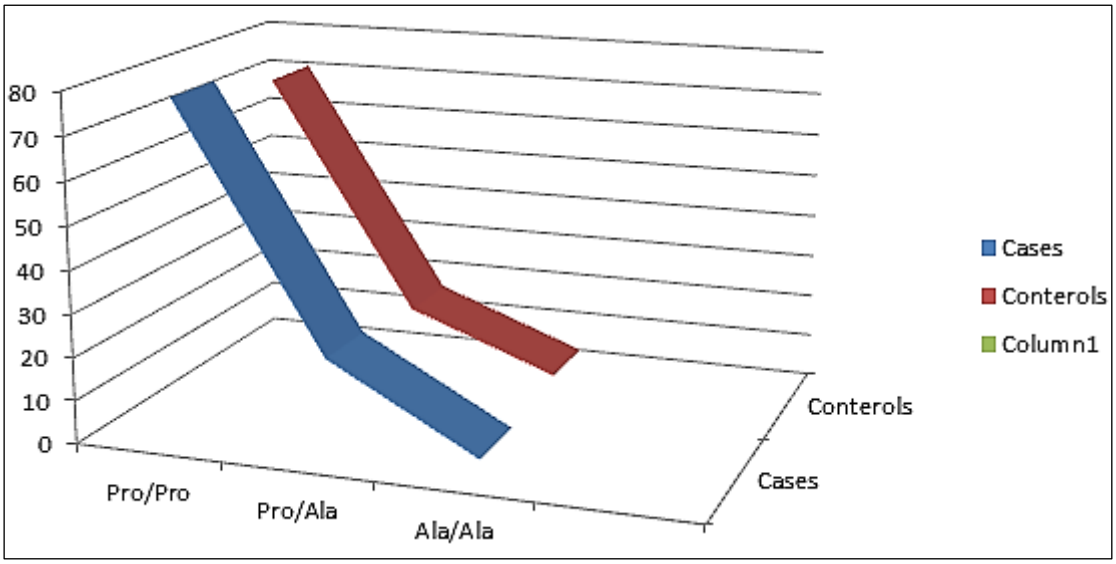

Fig. 2: *Genotype Distribution of the Gene ppay-2 Gene in Cases and Controls.*

There was statistically significant reduced risk of developing Diabetic -2 in those individuals who attain the Ala/Ala genotype (p<0.05 Or=0.80, 95% CI, 0.51–1.17).

DISCUSSION

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. The vast majority of cases of diabetes fall into two broad etiopathogenetic categories. In one category, type I diabetes, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes can often be identified by serological evidence of an autoimmune pathologic process occurring in the pancreatic islets and by genetic markers. In the other, much more prevalent category, type 2 diabetes, the cause is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. In the latter category, a degree of hyperglycemia sufficient to cause pathologic and functional changes in various target tissues, but without clinical symptoms, may be present for a long period of time before diabetes is detected [5].

This disease (T2DM) is a serious metabolic disease associated with an increased risk of premature death and substantial disability, largely mediated through its adverse effects on the vasculature. Prevalence of diabetes in adults worldwide was estimated to be 4.0% in 1995 and to rise to 5.4% by the year 2025. It is higher in developed than in developing countries. The number of adults with diabetes in the world will rise from 135 million in 1995 to 300 million in the year 2025. The prevalence of this disease has increased sharply during the past two decades in the world and is close to 6% and the World Health Organization estimate suggest that by 2025 there will be 300 million affected individuals worldwide [6,7]. The major part of this numerical increase will occur in developing countries. There will be a 42% increase, from 51 to 72 million, in the developed countries and a 170% increase, from 84 to 228 million, in the developing countries. Thus, by the year 2025, >75% of people with diabetes will reside in developing countries, as compared with 62% in 1995. In developing countries, the majority of people with diabetes are in the age group of 45–64 years.

In the developed countries, the majority of people with diabetes are aged >65 years. This pattern will be accentuated by the year 2025. There are more women than men with diabetes, especially in developed countries. In the future, diabetes will be increasingly concentrated in urban areas [8].

Type 2 diabetes mellitus is a complex metabolic disease that is caused by insulin resistance and β-cell dysfunction. It is commonly accepted that type 2 diabetes results, on the one hand, from population aging and, on the other hand, from adverse environmental factors of the modern world (i.e., high-caloric diets, physical inactivity, and a sedentary lifestyle) which favor the development of obesity. In fact, excess body weight represents a major risk factor for type 2 diabetes [9–11]. However, some 10% of type 2 diabetic patients display normal weight, and many obese subjects never develop type 2 diabetes, indicating that type 2 diabetes is not exclusively caused by environmental factors.

In addition, there have been reports that, the disease clearly represents a multifactorial disease, and several findings indicate that genetics is an important contributing factor [12,13]. Moreover, the disease has been reported to be characterized as polygenic disorder and generally could be thought of as a syndrome [14]. Over the past 2 years, genome-wide association scans have transformed the genetic landscape of type 2 diabetes susceptibility, with the current gene count close to 20 [15]. Some of the different genes studied to assess the risk of diabetic 2 in different ethnic back ground include *CAPN10* (11), *SLC2A2* (12) *KCNJ 11* (11) and *HNF4A* (13) are among others with positive associations.

Preoxisome proliferator-activated receptor gamma (PPAR*γ-2*) is a nuclear hormone receptor that plays a critical role in regulating adipocyte differentiation and the transcription of genes that are important for lipogenesis. In macrophages, the activated PPAR-*γ2* promotes the cellular efflux of phospholipids and cholesterol in the form of high density lipoprotein (HDL) [16,17]. PPAR-*γ2* is a key modulator of adipogenesis and insulin signaling [18]. PPAR-*γ2*, being a transcription factor, modulates the expression of several genes such as; adiponectin, leptin and resistin, which are involved in fatty acid metabolism, glucose homeostasis and insulin sensitivity [19]. Resistin is a small cysteine-rich secretory protein expressed in adipocytes and macrophages. It has been proposed that resistin provides a connecting link between obesity and insulin resistance [20]. In addition, it has also been shown to stimulate several pro-infl ammatory cytokines including tumour necrosis factor alpha (TNF-α) and interleukin twelve (*IL-12)* [21]. *PPAR-γ2* regulates the expression of resistin through several PPAR response elements (PPREs) present in the promoter region of the resistin gene. Since PPAR-γ2 are nuclear transcription factors regulating multiple genes involved in energy production, glucose and lipid metabolism, polymorphisms in these receptors may influence the pathology of numerous diseases including obesity, diabetes, atherosclerosis, inflammation and cancer [22].

So far, three different peroxisome proliferator activated receptor subtypes has been discovered: peroxisome proliferator-activated receptor-alpha, peroxisome proliferator-activated receptor-beta, and peroxisome proliferator-activated receptor-gamma (PPAR-γ2), have been identified [23,24]. The human *PPAR- γ2* gene is located on chromosome 3p25 and plays critical roles in regulating lipid metabolism, adipocyte differentiation, proliferation and insulin sensitivity [25]. *PPAR-γ2* has been shown to have roles in regulating genes involved in control of, uptake, transport, storage, and disposal of lipids, such as lipoprotein lipase, fatty acid transport protein, CD36, and adipophilin apart from involving in regulating glucose metabolism [25]. PPAR-γ2 also plays a key role in the entraining of adipose tissue lipid metabolism to nutritional state [26]. The *PPAR-γ*2 gene is therefore a promising candidate for metabolism syndrome [27]. Metabolic syndrome is the common name for a cluster of metabolic disorders that together represent an indicator of the risk for diabetes, heart disease, stroke and other cardiovascular conditions. This (MS) is characterized by a clustering of common chronic degenerative disorders such as hypertension, type 2 diabetes mellitus (T2DM), dyslipidaemia and obesity

[28], which has a strong genetic component. Variations in several candidate genes have been widely implicated in predisposing to these disorders. Peroxisome proliferator-activated receptor gamma (PPAR-*γ2*), a nuclear hormone receptor, controls adipocyte differentiation and regulates a number of genes associated with energy homeostasis [29]. To date, at least two naturally occurring mutations in this gene have been identified, which impair the function of PPAR-γ2. The *CG* mutation (*CCA-GCA* missense Mutation) in exon B of the *PPAR-γ2* gene leads to the substitution of alanine for proline at codon 12 (*Pro*12*Ala*) which has been found to modulate the transcriptional activity of the gene [30].

It has been clearly demonstrated that activation of *PPAR-γ2* results in an increase in the sensitivity of both the liver to insulin-mediated suppression of hepatic glucose production and insulin mediated skeletal muscle glucose uptake. In addition, PPAR-γ2 ligands are also shown to augment glucose disposal in peripheral tissues by increasing expression of the glucose transporter genes glucose transporter 1 (*GLUT1*) and *GLUT4* [31,32]. Moreover, it has been suggested that the *PPAR-γ2* gene affects the blood glucose level through enhancing insulin action on suppression of lipolysis, resulting in a decreased release of free fatty acids. Secondarily, reduced availability of free fatty acids would then permit muscle to utilize more glucose and liver to suppress glucose production more efficiently upon insulin stimulation.

The effect of *PPAR-γ2 Pro*12 *Ala* polymorphism and association of T2DM has been investigated by different authors for different population. Most of the results demonstrate the *pro* allele to be associated with increased risk and the *Ala* allele with reduced risk for type 2 diabetic mellitus. The result of the present study also demonstrated that Ala allele showed slightly reduced risk as compared to the pro allele. The *PPAR -12A* polymorphism has been reported to have a protective role in diabetes type 2 risk [33–37] which is similar to the present study. Although findings have not been uniform [38–41], a meta-analysis by Altshuler et al. determined that the presence of the 12*Ala* allele confers about 20% reductions in risk for diabetes [37]. Radha et al. found that *Pro* allele is a genetic risk factor for type 2 diabetes mellitus in Caucasians but not in South Asians [42]. Thus, they suggested that population difference plays an important role in susceptibility to diabetes mellitus. Doney et al. [43] and Memisoglu et al. [44] also reported the association of *pro* allele frequency of *PPAR- γ2* and type 2 diabetes mellitus. Similarly another report showed that the *pro* allele of this gene may predispose to diabetic nephropathy [45].

In contrast to this, Mancini et al. [46] and Ringel et al. failed to found a relationship between the *pro* 12 *Ala* polymorphism of *PPAR-γ2* gene and type 2 diabetes mellitus, the reason described was small sample size could have lost the statistical power to show significant association. Moreover, genetic background difference also may play its own role for discrepancy. Apart from that, population difference may affect the role of *Pro* allele as a risk factor for type 2 diabetes mellitus by many theories such as; the genetic background because of the gene-gene interaction or nutrition habits, and life style may affect PPAR-γ2 ligands like oleic acid as reported by [47].

A couple of reasons were the motives to conduct this study in a *PPAR-γ* 2 gene in north and south Gondar population. First, the majority of the genes identified thus far seem to affect diabetes susceptibility through cell dysfunction [48]. Second, the risk alleles tend to be common in the population, but their effect even if diabetes risk is relatively small [49]. However, this seemingly small risk association has not been studied ever since in the region and in the country due to varies reasons. Because recent genome-wide association (GWA) studies revealed convincing evidence for the contribution of genes to the pathogenesis of type 2 diabetes [50] and subsequent efforts in thoroughly and uniquely phenotyped cohorts provided first insights into these genes' pathomechanistic roles [51].

A wider study by including large sample size and area is warranted to confirm this

association further since; lack of resource has limited this study to concentrate on Gondar University, teaching hospital.

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